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APPARENT PLASMA HYPEROSMOLALITY IN ALCOHOLIC INTOXICATION

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APPARENT PLASMA HYPEROSMOLALITY IN ALCOHOLIC INTOXICATION

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ABSTRACT. The authors use the term "apparent osmolality" to refer to the measured value expressed in milliosmols/kg of water determined by means of osmometers-cryoscopes whose operating principle is based on the decrease in the freezing point as a function of the concentration of micro- or macromolecular particles in the medium. The apparent osmolality of plasma increases parallel to the level of alcoholemia; it is not accompanied by a parallel decrease in the measured resistivity of the plasma. The hyperosmolality caused by the ethanol molecule does not correspond to a plasma hypertonia.

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We have previously pointed out and studied the high frequency of polyuro- /1320*
-polylipsic syndromes following abstinence from alcohol among non-cirrhotic chronic alcoholics without kidney or heart disease [2,7].

The subjects remain capable of a normal secretion of A.D.H. as indicated by Decourt's test and their reactivity to clearance tests of free water. Polyur a and thirst, however, are not due to a diabetes insipidus.

In addition, we have found that the majority of chronic alcoholics, even before the clinical complications of cirrhosis, have a total blood volume and a blood plasma volume which are higher than normal. In addition, the increase in their serum-albumin space is particularly significant when these subjects are not polyuric [6].

Having observed as did Coreau [3] and Lecocq [16, 17] an increase in the cryoscopic delta of the plasma following acute or subacute alcoholization, we used this fact as a basis in asking whether or not it might possibly explain completely or in part certain problems affecting thirst and volemia of chronic alcoholics.

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*Numbers in margin indicate pagination in the foreign text.

Before discussing our results, some definitions are in order.

PRELIMINARY CONSIDERATIONS

The need for water in an adult man, physiologically translated by the sensation of thirst, is determined physically by an increase in the osmotic pressure of the medium.

The osmotic pressure corresponds to the mechanical pressure developed by the tendency of a solvent to pass through a membrane which separates this solvent from a solution with a higher concentration. The osmotic pressure, in its initial definition, therefore corresponds to a transfer of the solvent and not the dissolved substances across a membrane which is permeable to the solvent alone; it reflects a decrease in the relative concentration of the medium in the water; it causes a concentration gradient.

The total osmotic pressure of a medium is proprotional to the number of particles (molecules, ions of electrolytes, molecular aggregates) which it contains. It is independent of the size of these particles, their optical properties, their electrical charge, their valence or their chemical formula. The cell membranes of the tissues in the human organism are not strictly semipermeable to all the components of the extracellular medium with a complex composition, so that the total osmotic pressure corresponds to an ideal concept; its direct measurement, which necessitate a membrane that was permeable to the solvent alone is therefore impossible. /1321

CONCEPT OF OSMOLALITY

The relationship between the total osmotic pressure of the medium and its concentration in particles calls for a review of the definitions of molarity and molality, osmolarity and osmolality.

Molarity expresses the concentration in moles per liter of solution. Molality expresses the concentration in moles of dissolved substance per kilogram of solvent.

Hence, a molal solution is theoretically more dilute than a molar solution. Molarity and molality are similar when we are talking about dilute solutions. On the other hand, they become increasingly different as the dissolved substances increase in specific volume.

The term "osmol" was introduced for the first time in 1934 by Gamble [8]. The osmol is a unit of osmotic pressure used in medical biology. It represents the mass of 6.023×10^{23} osmotically active molecules of a substance in an aqueous solution. It is assumed to correspond to the osmotic pressure exerted by a gram-molecule of a substance dissolved in one liter, i.e., one kilogram, of pure water (22.4 atmospheres at 0°C).

In the case of a monoatomic substance, the osmol corresponds to the atomic weight expressed in grams.

For a nondissociable substance such as urea, glucose, ethyl alcohol, etc., the osmol corresponds to the gram molecule.

When we are speaking of a dissociable molecule, the osmol is defined with an assumption of total dissociation. If the molecule dissociates into X particles, the osmotic pressure will be multiplied by X. Thus, in the case of sodium chloride, if the dissociation is total, the number of osmols is two.

In clinical biology, the term milliosmol (abbreviated mOsm or mosM) is used, which corresponds to 10^{-3} osmols (Osm or osM).

Osmolarity corresponds to the molecular concentrations of all of the osmotically active particles per liter of solution.

Osmolality corresponds to the molecular concentrations of all of the osmotically active partilces per kilogram of solvent.

Osmolality reflects the evaluation of osmotic relationships more precisely than does osmolarity, because it is the ratio of the number of dissolved particles to the number of molecules of water between them. The osmolality differs from molality because it corresponds to a concentration of particles and not to a molecular concentration.

In reality the dissociation of a molecule into osmols is never complete due to the interaction of the solvent and the attraction of the ions.

We can write that:

Osmolality = ϕ n molality, where

ϕ is the osmotic coefficient, or the percentage of the deviation with respect to ideal behavior with total dissociation without interaction of the solvent or attraction of the ions.

n is the number of particles that the totally dissociated molecule can form.

The best synonym for osmolality is osmotic concentration. It should not be confused with the term "osmotic pressure." These are the definitions accepted by the majority of physical chemists.

In a recent paper, Dormandi [5] defines true osmolality as a property of the solvent and not of the dissolved substances. He defines the calculated osmolality as the sum of the specific concentration of the dissolved substances, assuming total dissociation. He gives the name of "measurable osmolality" to the value of osmolality which exists in the complex biological medium as a function of an incomplete dissociation and interactions between the solvent and dissolved substances.

On the other hand, Johnson [13] gives osmolality the following definition: he defines it as the molality of an ideal substance dissolved in water in sufficient quantity to produce the same osmotic pressure and the same depression of the freezing point as the sample.

This substance can be neither an electrolyte nor a substance capable of dissociation or association, nor of interaction with water. The quantity of dissolved materials which have an equivalent effect to one molecule of ideal substance is called an osmol.

CONCEPT OF EFFECTIVE OSMOTIC PRESSURE

This concept of effective osmotic pressure corresponds to the concept of efficacious osmotic pressure defined by Hamburger [10].

The majority of cell membranes allow the solvent and the dissolved substances to pass through. /1322

The effective osmotic pressure or tonicity is the attractive force exerted on the solvent by the molecules which do not pass through the membrane. It therefore corresponds to the pressure that results from a difference in concentration on both sides of a membrane. A difference in concentration of 1 milliosmol across a semipermeable membrane exerts an effective osmotic pressure of 17 mm Hg or 0.0224 atmosphere.

In order for a substance to exert an efficacious osmotic pressure between two compartments of an organism, it is necessary for it not to diffuse or to diffuse very slowly across the cellular membrane.

The cellular membrane is traversed by dissolved substances in variable amounts. As a consequence, they will not have an equal osmotic power. Moreover, various cellular membranes do not have the same permeability with respect to a given substance. This variation in the amount of diffusion also indicates that two solutions which have the same osmotic concentration will not necessarily be isotonic.

METHODS OF MEASURING OSMOLALITY

We have seen that the direct measurement of osmotic pressure is impossible in the case of biological solutions because of the impossibility of finding membranes that are permeable to the solvent alone. It is therefore necessary to have recourse to indirect methods, based on the following facts:

- when a molecule of a non-ionized substance is dissolved in 1 kg of water, the following colligative properties are modified;
- the freezing point of the solution is depressed by 1°86;
- the osmotic pressure rises by 17,000 mm Hg;
- the boiling point increases by 0°52;
- the vapor pressure decreases by 0.3 mm Hg.

Each of these properties can reflect the osmolality. Each of them has its advantages and disadvantages.

Ebullioscopy is of limited value because substances that are in solution in biological fluids are liable to be destroyed. Dormandi [5] recommends the determination of the vapor pressure, but this method is difficult to apply in clinical biology.

The determination of the freezing point is the method which will indicate the osmolality of biological fluids in the easiest and most sensitive fashion.

DETERMINATION OF THE OSMOLALITY OF A SOLUTION BY MEASURING THE DECREASE IN ITS FREEZING POINT.

This method is based on the combination of the generalized Raoult law and the Van t'Hoff law.

The freezing point of a complex solution which varies inversely with the molecular concentration is decreased when the osmolality increases. The measurement of the cryoscopic decrease in the plasma relative to water will allow the osmotic concentration of the plasma to be determined.

On the basis of the formula:

$$\Delta\theta = KN, \text{ where}$$

N represents the number of particles per kg of water, N being expressed as milliosmols;

K represents a factor that depends on the solvent. It is 0.001858 for water. Some authors use the value 0.00186;

we can then write: $N = \frac{\Delta\theta}{K}$

Two methods can be used:

- classical manual techniques, using the Beckmann cryoscope.

The osmolality values will be obtained by calculation on the basis of the measurement of the cryoscopic decrease of the plasma; if the latter is -0°56:

Osmolality: $\frac{0°56}{0.00186}$ = 301 milliosmols per kilogram of plasma water.

- by using modern cryoscopic osmometers which permit direct measurement of the osmolality in milliosmols.

- the osmolality of a solution is determined by comparison of its freezing point with that of sodium chloride solutions of known concentration and expressed in molal form.

It is conventional to say that 1 milliosmol per kilo produces an increase in the freezing point of 0.001858°.

Dormandi [5] estimates that these devices will allow a reading in millidegrees and not in milliosmols. He uses the term "osmolality recorded" to represent the value obtained in this manner, which can be translated in French "osmolalité enregistrée." /1323

In the course of this discussion, we shall use the term "apparent osmolality" to designate the concentration values determined on the basis of the freezing point; we shall do this for two reasons:

- on the one hand, because the interaction between the solvent and the dissolved substances affect the number of particles formed;

- on the other hand, because the number of particles thus determined is not a real reflection of the osmols which participate in the movement of the water in the intracellular and extracellular media of the human organism.

THE OSMOTIC COMPOSITION OF THE PLASMA IN THE PHYSIOLOGICAL STATE.

The total plasma osmotic composition of the plasma corresponds to the total number of existing particles:

- nondissociable micromolecules (such as glucose, urea, alcohol, acetaldehyde) and molecules of nondissociated electrolytes;

- ions furnished by the dissociation of molecules of ionizable electrolytes;

- molecules which are dissociated or not (such as proteins).

The diagram in Figure 1 shows the osmotic composition of plasma and demonstrates the quantitative importance of the various components in the

maintenance of osmotic pressure. The Cl^-, Na^+ and CO_3II ions play the predominant role and in the normal state are responsible for 85% of the total osmotic pressure.

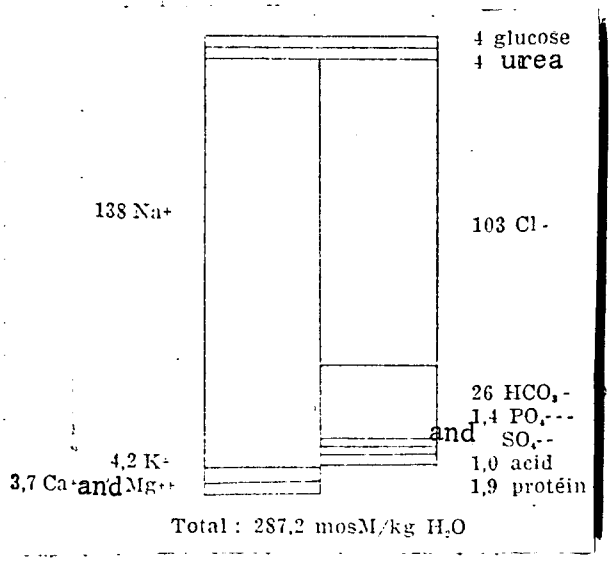

Figure 1. Graphic Representation of the Osmotic Composition of Plasma in the Normal State, After Abele [1]. The values are expressed in mosM/kg of water.

The proteins play only a small part; urea and glucose play a minimal role: 2 milliosmols for urea and 4 milliosmols for glucose. Urea and glucose are molecules which readily diffuse across the membranes of various compartments in the organism; the effective osmotic pressure which they exert at physiological concentrations is therefore less than that exercised by substances with slow or zero penetration into the cellular medium, such as the Na^+ ion.

OSMOLALITY VALUES OF PLASMA AND URINE IN THE NORMAL STATE.

The osmolality value of the plasma differs from that of the osmolarity due to the presence of proteins which have a high specific volume: the plasma osmolality will be slightly higher than the osmolarity.

In the normal state, the value of the cryoscopic delta, determined manually, varies between -0°55 and -0°57, corresponding to an osmolality of 295 to 306 mosM per kilogram of plasma water.

For Sunderman [23], the values are from -0°535 to -0°555 with an average of -0°547.

For Gram [9], they are from -0°555 to -0°570 with an average of -0°562.

Hamburger [10] uses a corrected value for the measured cryoscopic delta, obtained by subtracting from the measurement the number of hundredths of a degree corresponding to the molecules of glucose and urea added chemically.

The modern instruments, called osmometers in an imprecise fashion, which allow direct reading in milliosmols by using the principles of cryoscopy give the following values for various experimenters, obtained on the basis of various osmometers; they are expressed in milliosmols per kilogram of plasma water or serum water:

Lindeman [18], 289 to 308 mosM/kg of water.

Hendry [11], 290 mosM/kg of water. (S.D. ± 4).

Roberts [21], 280 ± 10 mosM/kg of water.

According to Abele in "Physical Chemistry Review" [1], 287.2 mosM/kg of water with as normal variations: 285 to 290 mosM/kg of water.

In the case of urine, the values of osmolarity and osmolality are similar.

The osmolality values, in the case of 24-hour urine, are as follows: /1324

Lindeman [18]: 967 to 1342 mosM/kg.

Jacobson [12]: 855 to 1335 mosM/kg.

COMPARISON BETWEEN THE VALUES FOR THE OSMOTIC COMPOSITION OF THE PLASMA OBTAINED DIRECTLY BY CRYOSCOPY AND BY MEANS OF CHEMICAL DOSES.

The values given by cryoscopy are lower in the physiological state than those established by calculation on the basis of the concentrations obtained from chemical doses. This calculation supposes that the dissociation of the electrolytes is total, which is not really the case and does not allow for the osmotic coefficient in the case of the molecules which are nondissociable or are ionizable.

Thus, we have seen that the following relationship exists between osmolality and molality:

$$\text{Osmolality} = \phi \, n \, \text{molality}.$$

However, an empirical correspondence is possible because the degree of dissociation of the electrolytes is constant within the limits of physiological concentrations.

Moreover, in current practice, it is assumed that nondissociable substances (urea, glucose) compensate (in the normal physiological state) for the loss of ionic milliosmols due to incomplete dissociation of the electrolytes.

OSMOLALITY AND RESISTIVITY.

Osmolality is the reflection of the number of particles in the plasma.

The resistivity, which is the reciprocal of the conductivity, depends on the number of free ions trapped in the solution, with the nondissociated molecules being without any electrical influence.

The resistivity value is inversely proprotional to the value of the electrolytemia; a decreasing resistivity corresponds to an electrolytemia which increasing, so that plasma hypertonia results; increasing resistivity corresponds to electrolytemia which is increasing so that plasma hypotonia results.

PROTOCOL OF THE EXPERIMENTS.

1. Recruitment of the Population Studied.

The study involved alcoholics, all men, being treated at the Alcohol Disintoxication Service of the Charity Hospital. The blood samples were taken at the time of admission to the service. The urine collections were conducted immediately afterward. Hence, the urine studies were conducted with urine from a single miction.

2. Methods Used for Blood Dosages.

(a) Alcoholemia:

This is determined on the basis of the total blood collected on sodium fluoride with the usual precautions (no alcohol-based antiseptic to clean the material and the skin of the patient).

The technique employed is that of Nicloux modified by Postic [20], official in France, but of less specificity than the enzyme method (principle: distillation followed by determination using reduction of potassium bichromate by the ethyl alcohol present in the distillate).

Normally, following any alcoholization, one can find values of 0.100 g/l caused by volatile-reducing substances trapped in the distillate.

Studies of plasma alcoholemia were also carried out with certain patients.

The tests of the blood urea and glycemia were carried out with the correction of fluoridated total blood collected for alcoholemia. These tests were performed with the aid of a Technicon autoanalyzer.

(b) Blood Urea:

Colorimetric examination using diacetylmonoxime in an acid medium.

Normal values: 0.10 - 0.30 g/l.

(c) Glycemia:

Tests based on the reduction of potassium ferricyanide in an alkaline medium.

Determination of the total glycemia (hemolysis of the blood by dilution with distilled water prior to dialysis).

Normal values: 0.70 to 1.0 g/l.

(d) Determination of the Hematocrit:

Performed with the aid of a Clay-Adams micro-centrifuge. The following measurements were carried out with plasma obtained by centrifuging the collected blood mixed with heparin [0.5 mg of dry heparin (lithium salt) for 10 ml of blood or 0.1 ml of a 5% heparin solution of Choay or Fournier]. It is necessary to avoid any venous stasis caused by prolonged application of the tourniquet. /1325

(e) Protidemia:

This is determined with the aid of the Technicon autoanalyzer using biuret reagent.

Normal values: 67 ± 7 g/l.

(f) Plasma Osmolality:

This is determined with the aid of a Fiske cryo-osmometer calibrated with molal solutions of sodium chloride (100 and 500 milliosmols/kg of water). Regardless of the nature of the solution it was never necessary to perform calibration of the apparatus with solutions obtained by dilution of a stock solution of sodium chloride. It was necessary that they not contain any particles in solution. These comments are valid for biological samples (plasma, serum, urine). The equipment used to collect the samples, as well as the laboratory glassware, had to be extremely clean. The hemolysis of the plasma was eliminated inasmuch as it does not interfere because the lysed red blood cells have a nearly equal osmolality. The measurements were performed rapidly because storage of the samples leads to a drop in value.

According to Johnson [13], the values are stable for 3 hours at 20° and 10 hours at 4°.

The normal values (without correction, as a function of the amounts of urea and glycemia) were: 286 to 292 mosM/per kilo.

(g) Plasma Resistivity:

This was determined with the aid of the Phillips resistivimeter at 37°C.

The constant of the measurement cells was checked with the aid of a M/50 potassium chloride solution of known resistivity.

We merely recorded the measured resistivity. Corrections as a function of proteinemia are possible.

The normal values for the measured plasma resistivity were 67 to 72 ohms/cm^2/cm at 37°.

(h) Natremia:

This is determined in the plasma with aid of a Coleman flame photometer.

Normal values were 137 to 150 mEq/l (average value - 144 mEq/l).

NOTE: The difference between plasma and serum osmolality is small. It is due to plasma fibrinogen, with the heparin salt that is added playing a negligible role.

Coulson [4] finds a difference of less than 5 mosM/kg. In the case of plasma, we found values that were 3 mosM/kg higher than those for serum. Some authors prefer the serum, which congeals more regularly than the plasma.

3. Methods Used for Urinary Determinations.

(a) Urinary osmolality using a sample of urine collected in a clean vessel without addition of preservatives.

Johnson [13] recommends homogenizing the urine immediately prior to removing the samples intended for analysis; then the precipitated substances are dissolved by heating for 20 minutes at 37°C followed by rapid centrifuging.

(b) Urine density, determined with the aid of urodensimeters graduated for a temperature of +15°. When the urine temperature is different, it is necessary to make a correction in the number read on the densimeter scale of one thousandth for each 5° above or below 15°.

Normal values: 1018 to 1022.

RESULTS

Several points will be discussed in succession.

1. Cryoscopic Delta (Expressed in Milliosmols) of the Plasma and Alcoholemia.

The comparison of the values of the cryoscopic delta expressed directly in milliosmols and of alcoholemia on the basis samples collected upon admission of alcoholics to the hospital indicates the relationship described by Lecocq [16,17] and Coreau [3].

The comparison of these measurements performed on 253 subjects confirms that the presence of a certain number of moles of ethyl alcohol in the plasma or of intermediary products of its catabolism is accompanied by an increase in the apparent total plasma osmolality. These results, shown in Figure 2, clearly illustrate the relationship which exists between the two measurements:

when the alcoholemia is elevated the value of the apparent osmolality increases; when alcoholemia is on the order of 1 g/l, the increase in osmolality determined by calculation, considering that ϕ is equal to 1, is 21.8 mosM.

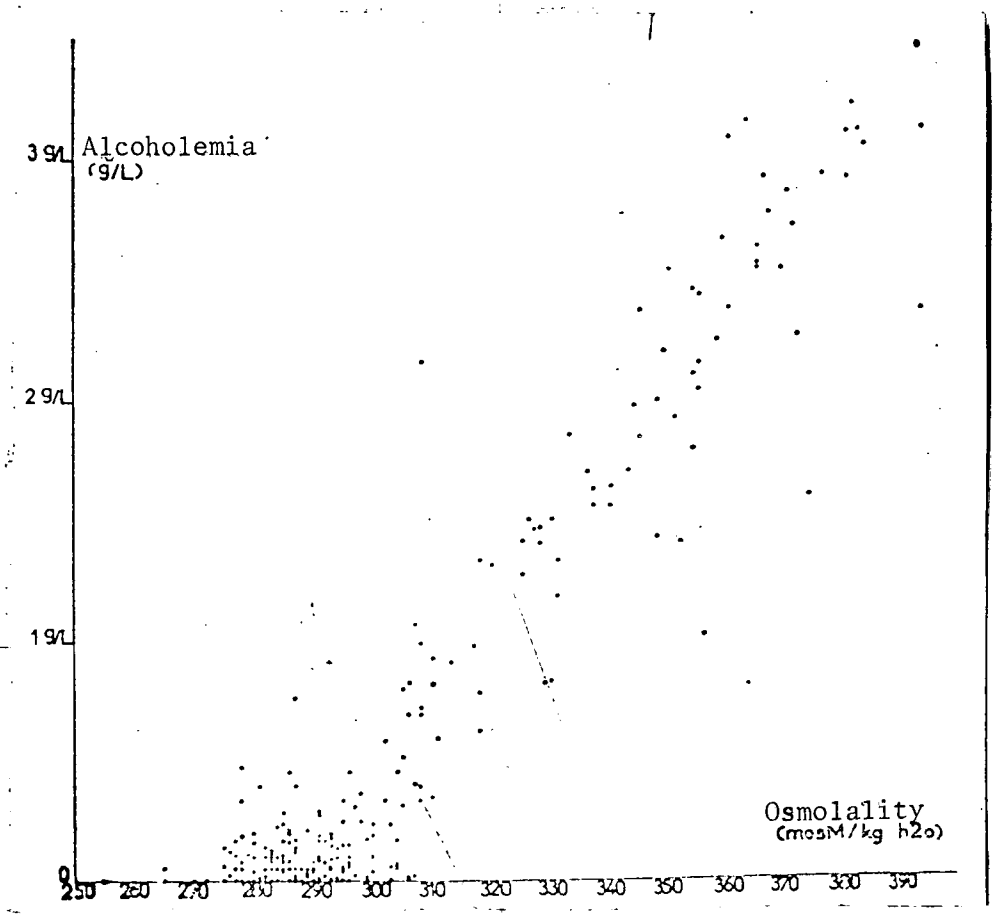

Figure 2. Variations in Alcoholemia and Osmolality in Chronic Alcoholics.

Figure 3 shows the values of osmolality for the same solution of sodium chloride to which we had added pure ethyl alcohol at respective concentrations of 1, 2 and 3 grams per liter. In an aqueous medium, *in vitro*, the proportionality existing between osmolality and concentration in ethyl alcohol is clear.

In Table 1, we have listed the values of the measurements made on 50 alcoholics at the time of their admission.

a Rf. malade	Urée sanguine b g/l.	Urée sanguine b Nombre mosM.* i	Glycémie c g/l.	Glycémie c Nombre mosM.* i	Alcoolémie d (sang total) g/l.	Alcoolémie d (sang total) Nombre mosM.* i	e Osmolalité apparente totale mosM/kg	f Osmolalité résiduelle mosM/kg **	Résistivité mesurée g à 37° ohms/cm² et cm	h Natrémie mEq/l.
1	0,24	4	1,10	6,1	0,74	16	328	301,9	71,4	144
2	0,11	1,8	0,95	5,2	0,83	18	312	287	70,7	150
3	0,13	2,1	0,84	4,6	0,88	19	313	287,3	72,2	144
4	0,12	2	1,14	6,3	0,94	20	374	345,7	68,4	141
5	0,09	1,5	0,96	5,3	1,01	21,9	306	277,3	70,6	N.D. ***
6	0,17	2,6	0,95	5,2	1,04	22,6	314	283,6	72	150
7	0,18	3	1,24	6,8	1,10	23,9	329	295,3	72	144
8	0,12	2	1,65	9,1	1,12	24,3	317	281,6	71,4	139
9	0,24	4	1,20	6,6	1,15	25	339	303,4	65,3	150
10	0,15	2,5	0,96	5,3	1,15	25	320	287,2	66,9	144
11	0,14	2,3	1,88	10,4	1,16	25,2	320	283,9	73	129
12	0,18	3	0,93	5,1	1,29	28	370	333,9	63,8	144
13	0,10	1,6	1	5,5	1,40	30,4	360	322,5	66,1	139
14	0,15	2,5	1,38	7,6	1,43	31	325	284,9	71,4	139
15	0,20	3,3	0,86	4,7	1,43	31	330	291	73	139
16	0,10	1,6	0,66	3,6	1,62	35,2	336	295,6	72,2	N.D.
17	0,10	1,6	0,76	4,2	1,72	37,3	331	287,9	66,1	141
18	0,18	3	2,07	11,5	1,78	38,6	332	278,9	69,1	147
19	0,15	2,5	0,68	3,7	1,84	40	324	277,1	73	139
20	0,09	1,5	0,98	5,4	1,84	40	357	301,1	71,4	141
21	0,15	2,5	0,80	4,4	1,99	43,2	328	277,9	69,9	N.D.
22	0,10	1,6	1,08	6	2,01	43,6	325	273,8	72	144
23	0,20	3,3	1,08	6	2,04	44,3	322	268,4	68,4	N.D.
24	0,10	1,6	1,02	5,6	2,16	46,9	346	291,9	72	139
25	0,23	3,8	1,14	6,3	2,18	47,3	331	273,6	73	150
26	0,4	6,6	0,82	4,5	2,18	47,3	354	295,6	73	141
27	0,10	1,6	0,82	4,5	2,32	50,4	350	293,5	70,6	N.D.
28	0,10	1,6	1,68	9,3	2,35	51	357	295,1	72,2	139
29	0,18	3	0,82	4,5	2,41	52,3	370	310,2	69,9	N.D.
30	N.D.		N.D.		2,58	56	369	N.D.	N.D.	N.D.
31	N.D.		N.D.		2,60	56,5	365	N.D.	N.D.	N.D.
32	0,15	2,5	0,80	4,4	2,67	58	359	289,8	69,9	144
33	N.D.		N.D.		2,67	58	365	N.D.	N.D.	N.D.
34	0,10	1,6	0,92	5,1	2,70	58,6	360	295,7	69,7	141
35	N.D.		N.D.		2,70	58,6	359	N.D.	N.D.	N.D.
36	0,13	2,1	1,28	7,1	2,76	60	366	289,8	72	141
37	0,20	3,3	0,91	5	2,77	60,2	374	305,5	67,6	144
38	N.D.		N.D.		2,90	63	370	N.D.	N.D.	N.D.
39	0,16	2,6	0,84	4,6	2,93	63,6	382	311,2	N.D.	N.D.
40	N.D.		N.D.		2,96	64,3	366	N.D.	N.D.	N.D.
41	N.D.		N.D.		2,96	64,3	380	N.D.	N.D.	N.D.
42	N.D.		N.D.		3,10	67,3	382	N.D.	N.D.	N.D.
43	N.D.		N.D.		3,15	68,4	380	N.D.	N.D.	N.D.
44	N.D.		N.D.		3,16	68,6	382	N.D.	N.D.	N.D.
45	0,10	1,6	0,80	4,4	3,16	68,6	366	281,4	65	150
46	0,10	1,6	0,96	5,3	3,16	68,6	364	288,5	63	144
47	N.D.		N.D.		3,19	69,3	363	N.D.	N.D.	N.D.
48	N.D.		N.D.		3,27	71	381	N.D.	N.D.	N.D.
49	N.D.		N.D.		3,27	71	365	N.D.	69,1	137
50	0,18	3	1,29	7,1	3,61	78,4	392	305,5	72	144

/1327

Table 1. Key: a-no. of patient, b-blood urea, c-glycemia, d-alcoholemia (total blood, e-apparent total osmolality mosM/kg, f-residual osmolality, mosM/kg**, g-resistivity measured at 37° ohms/cm^2 and cm, h-natremia mEq/l, i-Number mosM*.

*The number of milliosmols of urea, glucose, and ethanol was obtained by dividing the amount expressed mg/l by the molecular weights. These measurements were carried out with the total blood.

**Residual osmolality = total apparent osmolality - the number of milliosmols due to urea + glucose + ethanol.

***N.D. = Not Determined

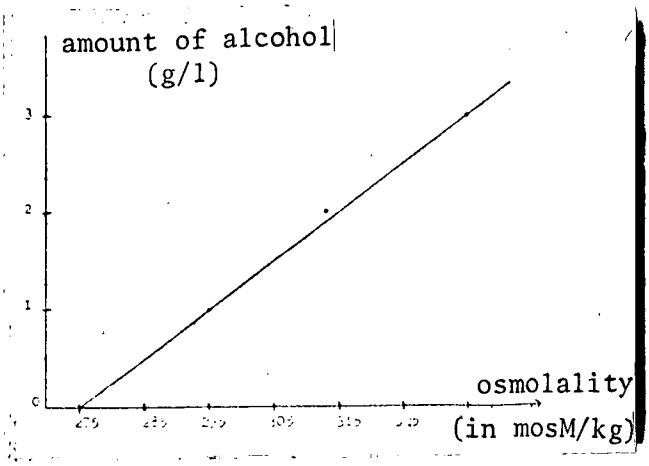

Figure 3. Osmolality Relationship. Concentration in alcohol for an aqueous solution of sodium chloride of a given concentration.

For 12 of them, we merely carried out the determinations of the apparent plasma osmolality and calculated the residual osmolality following subtraction of the number of milliosmols[1] corresponding solely to the value of alcoholemia; the amount of blood urea and glycemia were not determined, but we can say that the correction that would have to be made would be approximately 6 to 7 milliosmols/kg.

For the 38 others, we found the following values in nearly all cases: blood urea, glycemia, natremia; measurement of apparent total plasma osmolality; /1328 calculation of the residual osmolality after subtracting the number of milliosmols due to urea, glycemia and alcoholemia and established by calculation the basis of chemical measurements.

We can see that for nearly identical alcoholemia values the value of the apparent osmolality varies. These differences were found following determination of the effective apparent osmolality obtained by subtracting the osmalalities of the substances that diffuse rapidly, such as urea, glucose and alcohol. The catabolites which were not contributed by the absorbed ethyl alcohol may be responsible for these variations.

2. Measured Resistivity and Apparent Osmolality of the Plasma - Alcoholemia.

While the alcoholemia and apparent osmolality of the plasma vary in the same direction, the measured resistivity remains in the zone of physiological values when the alcoholemia is increased.

[1]The number of milliosmols is obtained by dividing the amount of the substance expressed in mm/l by the molecular weight; this calculation, which corresponds to a molar concentration, is valid when the osmotic coefficient ϕ is equated to 1. More strictly, we would have had to express the results of the measurements in molality; we did not do this because the measurements were made on the total blood; in any case, the differences are very small.

The average value of the resistivity that was measured for 50 alcoholics having zero alcoholemia when admitted was 70.4 ohms/cm^2/cm at 37° with the following as extreme values: 67 and 73 ohms/cm^2/cm.

The average value of the resistivities measured in 37 alcoholics with alcoholemia above 1 g/l was 68.2 ohms/cm^2/cm.at 37°, with the following as extreme values: 63 and 73 ohms/cm^2/cm.

The natremia values reflect those of resistivity quite faithfully. The osmolality values vary inversely. However, there were not significant ionic modifications in the composition of the plasma in these subjects; only 4 of them had a measured resistivity that was less than 66 ohms/cm^2/cm at 37°; these were subjects Nos. 9, 12, 45, and 46, whose results are shown in Table 1. The measurements of protidemia and the hematocrit value indicate a hemoconcentration (protidemia above 90 g/l) in two cases (Nos. 12 and 46).

The degree of dissociation of the electrolytes in the solution which will determine on the one hand the value of the osmolality as a function of the number of particles or ions formed and on the other hand that of the resistivity as the function of the number of dissociated ions is constant within the limits of normal biological concentrations. It depends on the concentration and the nature of the electrolytes, the temperature, and the solvent as well. While water allows good dissociation of electrolytes, alcohol is a little less favorable from the ionization standpoint. We wanted to determine, by using an aqueous solution of sodium chloride to which some pure ethyl alcohol had been added in order to obtain amounts of 1, 2, and 3 g/l so frequent in our patients, whether the measured resistivity could be modified; we did not find any variation in resistivity.

The measurements we carried out on the plasma of alcoholic subjects did not appear to be falsified by the presence of ethyl alcohol.

Hence, we can say that the apparent hyperosmolality of our alcoholics was not frequently correlated with a plasma hypertonia.

3. Alcoholemia - Apparent Plasma Osmolality; Apparent Osmolality and Urine Density.

Each time that it was possible, we collected the urine (with the subject's permission) at the same time as we collected the blood.

In these urines, we studied the relationship between urine density and apparent urinary osmolality.

In 30 alcoholics with zero alcoholemia upon admission and an average value of apparent plasma osmolality of 288 mosM/kg, the average value of urinary density was 1019 with 1007 and 1034 as the extreme values. The average value of the apparent urinary osmolality was 720 mosM/kg of water with 205 and 1430 mosM/kg of water as extreme values.

In 25 alcoholics with alcoholemia above 1 g/l on admission and a mean value of apparent plasma osmolality of 347 mosM/kg, the average value of urine density is 1011 with 1003 and 1027 as the extreme values. The average value of the apparent urinary osmolality is 342.1 mosM/kg of water with 130 and 760 mosM/kg of water as extreme values.

High alcoholemia, low urine density, low apparent urinary osmolality are all associated, however; in four subjects, this relationship was not found.

In subject No. 20, the glycemia of 2.07 g/l could explain the higher value of urine density. For the other cases, any explanation would appear to be difficult.

Table 2 gives these data.

COMMENTS /1329

The shortcomings of our non-experimental research consist in the fact that we were unable to determine precisely the quantity of alcohol ingested, the amount of water absorbed at the same time and the time of absorption of alcohol relative to the blood sample and the urine collection.

These studies, however, do provide some explanations.

No of Alcoholics in Table 1	Alcoholemia (g/l)	Urinary Osmolality mosM/kg	Urine Density
5	1,01	453	1015
7	1,10	130	1003
8	1,12	267	1016
11	1,16	510	1018
12	1,29	760	1022
13	1,40	120	1003
14	1,43	267	1008
15	1,43	243	1009
16	1,62	677	1027
17	1,72	150	1004
18	1,78	744	1023
19	1,84	184	1006
20	1,99	713	1025
23	2,04	220	1007
24	2,16	304	1008
27	2,32	225	1008
28	2,35	282	1008
29	2,41	104	1005
32	2,67	210	1005
34	2,70	130	1004
36	2,76	359	1011
37	2.77	595	1016
44	3,16	272	1007
49	3,27	373	1009
50	3,61	262	1006

Table 2. Values for Osmolality and Urine Density as a Function of Alcoholemia and 25 Alcoholics.

1. Decrease of the Cryoscopic Delta of Alcoholics and Plasma Hypertonia.

A drop in the cryoscopic delta corresponds to an increase in the number of milliosmols or the apparent osmolality of the plasma as determined with the aid of modern cryoscopic osmometers.

In 1954, Coreau [3], due to the disturbances in the cryoscopic delta in the acute alcoholic state, wrote that the presence of alcohol in the blood causes modifications in the form of hypertonia which is proportional to the degree of alcoholemia.

Lecocq [17] also indicates that subacute alcoholic intoxication causes a drop in the freezing point of the plasma. In 1961, he mentions that the lowest amounts are quite often accompanied (on the days that follow) by delirious crises caused by sudden abstinence, despite therapy (ethylotherapy I.V., vitamins and also possibly neuroleptics or cortisone). Ordinarily, a clear return to normal is observed after the cure, but the cryoscopic delta remains lower than normal and appears to be linked to a hypertonia which does not disappear until later. This hypertonia following the cure would not suffice to explain the low values of the delta that were observed in certain alcoholics prior to treatment. The presence of moles of ethyl alcohol, in more or less strong doses, is the major cause of this. In 1963, it seemed that the measurements of the delta indicate profound alcoholic impregnation rather than true hypertonia.

In fact, it appears likely that the hyperosmolality of alcoholized plasmas only rarely causes a true hypertonia; we have seen that the measured resistivity remains constant in practically all of our subjects.

The definitions of molality fall into the area of physical chemistry. The concepts of osmolality and isotonia and biological.

The isotonia of a solution is not determined by a physical examination but a biological one -- the absence of lysis of red blood cells, for example. It is conventional to transpose the language of the chemists to the field of biology. This results in confusion in the mind of certain clinicians.

The apparatus refered to as "osmometers" are generally merely devices for determining the decrease in the freezing point. They only indicate the characteristics of concentration in micro- or macromolecular particles in a medium and merely allow an estimate of the result which is the osmolality.

If we wish to avoid confusing isotonia and isoosmosis, we must guard against transposing purely physical data to biology. Cryscopy is nothing more than a physical examination. Even if membranes which are semipermeable to water are available, allowing direct measurement of the osmotic pressure of the medium, it must not be forgotten that the living cell cannot be compared to a semipermeable membrane.

The degree of decrease in the freezing point of various saline or sugar solutions, provides information about their concentration but does not give any detail regarding their effects vis-à-vis the red corpuscles; a solution of urea which has the same cryoscopic delta as the plasma is hypotonic with respect to the red blood cells which are hemolyzed as rapidly as /1330
they are in the presence of distilled water. Recall that the isotonic concentration of alcohol is 13.8 g/l.

Hence, there is no correspondence between isotonic concentration and that of isoosmosis, and between hypertonia and hyperosmolality determined using an application of Raoult's law.

2. Cryoscopic Delta of Non-Habitual and Chronic Alcoholization.

In 1963, Roberts [21] demonstrated that the ingestion of alcohol has different effects as far as modifying the plasma cryoscopic delta depending on whether it was carried out by a normal subject or a chronic alcoholic: the value of the apparent plasma osmolality is higher and more prolonged

after a given alcoholization in the habitual drinker than in the normal subject. His sampling of alcoholics, after admission, showed a state of severe dehydration. The highest increases in osmolality among the chronic alcoholics were due to an increase in diuresis by inhibition of the antidiuretic hormone caused by alcohol. This is the explanation proposed by this author, who recognizes the value of ethyl alcohol as a treatment for refractory edemas.

One might perhaps object that this more significant increase in apparent plasma osmolality among the chronic alcoholics was due to a retarded catabolism of ethyl alcohol by reason of a drop in the activity hepatic alcohol dehydrogenase. Schwarzmann [22] has in fact demonstrated a reduced activity of alcohol dehydrogenase by a factor of one half relative to its normal activity in 61% of the cases among 27 known alcoholics without hepatic damage.

In fact, we can say the following:

- among 30 chronic alcoholics who showed zero alcoholemia following admission, we determined the apparent plasma osmolality to have an average value of 288 mosM/kg, while among our normal subjects this value was 286 to 292 mosM/kg;

- among the severe chronic alcoholics showing a polyuropolydipsic syndrome, studied by Bel [2], there is a characteristic average osmolality of 294 mosM/kg;

- the action of alcohol on the increase in diuresis in alcoholics who are severe but well hydrated, is clear. This will be discussed in the following section.

It must not be forgotten that the diffusibility of ethyl alcohol in the organism is increased. The doses of ethyl alcohol in the total blood and the plasma show a similar value when the dose is increased; this indicates that the alcohol diffuses rapidly in the cells and does not exercise an effective osmotic pressure. The diffusibility of ethyl alcohol in the organism varies, however, depending on the tissues or the various biological fluids because the latter are not equally rich in free water. The alcohol content of the tissues is inversely proportional to their richness in fat and proportional to their vascularization and their water content.

Van Heck et al. have established that the ratio of diffusion to blood concentration/concentration in organs or fluids was on the order of 0.75 for urine, 0.79 for L.C.R. and 1.37 for the brain. Hence, ethyl alcohol is capable of exercising a relatively important osmotic effect on the nervous tissue and of causing cellular suffering following dehydration.

3. Apparent Density and Osmolality of Urine as a Function of Alcoholization.

The sample of polyuropolydipsic chronic alcoholics, deprived of ethyl alcohol, in whom we studied the dynamics of hydroelectric perturbations in 1965 (Bel [2]) was characterized by urinary hypotonia: a urine density less than 1010.

The population of alcoholics who were not deprived but maintained alcoholemia above 1 g/l (25 subjects) could be divided as follows:

- 18 subjects with a urine density less than 1011,

- 7 subjects with a urine density above 1016.

In this second group of subjects, there was a hypotonic polyuria in the 24 hours following their hospitilization without there being any reabsorption of alcohol.

A priori, one might think that the polyuria of our alcoholics was not of a pure type: osmotic or aqueous.

Two phenomena could be superimposed:

- an osmotic polyuria caused by a non-sodium plasma hyperosmolality and caused by the proximal reabsorption of the water by virtue of the presence in the filtrate of non-reabsorbable substances (ethyl alcohol or its metabolites);

- an aqueous polyuria resulting from the inhibition of the antidiuretic hormone (ADH) by alcohol.

It appears that in the majority of cases the inhibition of the anti- /1331
diuretic hormone is the predominant phenomenon.

i	j	a Heures	Valeur b moyenne de l'alcoolémie en g/l.	c Diurèse en ml	d Densité	e Osmolalité en mosM/kg	Résistivité mesurée à 37° ohms f cm²/cm	Créatinurie en mg/l. g	Urée en g/l. h
Malade I	Avant	H - 10'			1019	626	32,6	148,85	6,5
	Au cours de perfusion k	HO to H 195'	0,40	340	1008	260	72	46,7	2,2
		H 195' to H 330'	0,80	190	1005	153	129,2	27,2	1,6
		H 330' to H 365'	1	410	1005	183	106,4	24	1,6
		H 365' to H 520'	1,40	680	1005	175	121,6	18,75	1,0
Malade II l	Avant j	H 10'		1.030	1008	322	76	570	6
	Au cours de perfusion k	HO to H 150'	0,10	1.000	1005	190	98,8	300	2,2
		H 150' to H 400'	0,63	1.170	1004	214	91,2	210	1,8

Table 3. Nature of the Urine Emitted Following Ethanolization Test in 2 Patients (Intravenous Perfusion of 100 g of Ethyl Alcohol in 8 Hours). Key: a - hours, b - average value of alcoholemia in g/l, c - diuresis in ml, d - density, e - osmolality in mosM/kg, f - resistivity measured at 37°, ohm cm^2/cm, g - creatinuria in mg/l, h - urea in g/l, i - Patient I, j - Before, k - during perfusion, l - Patient II.

Since our method of experimentation exhibits several inconveniences that we have mentioned above, we plan to determine (in urine with a density equal to or greater than 1015) in no subjects with alcoholemia above 1 g/l, the degrees of natriuria, chlorúria, alcoholuria and creatinuria. In fact, we can achieve several improvements with respect to the conditions for relieving aqueous polyuria.

We have been able to subject 2 subjects to tests of ethanolemia caused by intravenous perfusion of 100 g of ethyl alcohol in an isotonic sodium

chloride medium. The perfusion of alcohol causes the secretion of hypotonic urine when the value of alcoholemia is still relatively low; this polyuria is therefore unrelated to the apparent hyperosmolality of the plasma determined by the presence of moles of ethyl alcohol.

Table 3 summarizes the characteristics of these urines which become increasingly hypotonic as the amount of ethyl alcohol which is perfused becomes greater. The urine becomes more and more dilute and creatinuria, osmolality and density decrease, while resistivity increases. Hence, we are dealing with aqueous diuresis.

Roberts [21] prevents this aqueous polyuria by inhibition of ADH with the aid of sodium chloride. The need for salt which is displayed by beer drinkers has been known for a long time. (Mach [19]: "It is no accident that pretzels and salted radishes are found on bars.")

In those perfursions which produce acute ethanolization, the isotonic sodium chloride does not prevent the inhibition of ADH.

This polyuria develops from the exogenic water and the water in the body. Drinkers of beer and wine are also drinkers of water, and excessive drinkers are polydipsic if their alcoholization (and this is the rule) is not limited to the ingestion of spirits or pure alcohol.

This intake of solvent will allow more or less total complete compensation /1332
for the loss of water caused by this water diuresis through inhibition of ADH. The calculation of the volume of urine excreted by two chronic alcoholics, normally hydrated, following a test of provoked ethanolization performed under superposable conditions, indicates that subject II has a more significant diuresis than subject I and this is true although he appears to metabolize more rapidly the ethanol which is perfused since his alcoholemia remains essentially lower.

It therefore appears that inhibition of ADH by ethanol plays a major role in the dehydration of alcoholics, that this inhibition is not in proprotion to the blood alcohol concentration, and that each individual has his own reactivity.

4. Parallels Between the Apparent Hyperosmolality of the "Hyperosmolar" Coma of the Diabetic and the Hyperosmolality of Alcoholics.

The relationship of hyperosmolality to secondary cellular dehydration are well known in pathology and theraputics. It is for this purpose that rapid perfusions of urea are used in the treatment of cerebral edema and glaucoma (urea, in the normal physiological state, possess a negligible osmotic role by reason of the ease with which it diffuses in fluid compartments. However, its extra- and intracellular distribution is not immediate and the hypertonia thus created will lead to cellular dehydration.

In a recent publication, Laroche et al. [15] prefer to designate the hyperosmolar comas of diabetics by the term "coma by dehydration" or strictly "comas with hyperosmolality." Why is this? They feel that it is dehydration which appears to play the major role in the development of these comas.

These comas occur in aged subjects, afflicted with benign or malign diabetes, suddenly aggravated by some cause, especially an infectious one with development of thirst and polyuria. They are also observed following various accidents capable of causing problems with regulation of glycemia and dehydration (pancreatites, vascular, myocardial or cerebral accidents).

The coma develops progressively after a phase apathy and abstinence. It is a wakeful coma with reaction to light stimuli, various neurological symptons (extrapyramidal hypertonia, meningeal symptoms, Babinski signs) and considerable problems with vegetative activity (very high fever, irregular T.A., no dyspnea of Kussmaul).

The clinical symptoms of cellular dehydration are always very clear: persistence of skin folds, hypotonia of the eyeballs, dryness of the tongue.

The biological symptoms are the following:

- hyperglycemia (most often above 10 g/l);
- glycosuria, always very high;
- absence of acido-ketosis;

- significant ionic disturbances: hypernatremia (above 150 mEq/1), hyperchloremia, kaliema, low or normal;

- increased blood urea;

- plasmatic hyperosmolality (capable of reaching 450 milliosmols).

This hyperosmolality is caused by an increase in glycemia, uremia, and natremia.

What is the case of this coma?

The hyperglycemia which develops gradually can cause osmotic diuresis indicated by pronounced polyuria which causes a compensatory polydypsia and which is also unresponsive to the action of ADH.

The glucose, by reason of the insulin shortage, is unable to enter the extracellular and intracellular spaces because its penetration into the cell is limited and it will play a not negligible osmotic role as a function of the quantity in which it is given. This is what takes place in the entire organism except at the level of the encephalon where the penetration of glucose into the cells takes place freely, eliminating the osmotic effects of hyperglycemia and not allowing the problems involving consciousness to be attributed to this hyperglycemia. This osmotic polyuria, if it is not compensated for will cause a state of extracellular dehydration. Aggravation of hypertonia will be created on the one hand by an increased reabsorption of sodium, due to hyperglycemia independently of aldeosterone (Larcan et al. [14]), and on the other hand because of the rapid rise in uremia.

The result is a cellular dehydration with problems involving consciousness.

In what way is this coma caused by dehydration with hyperosmolality comparable to alcoholic coma?

Clinically speaking, not a great deal, since alcoholic coma is rapid in its onset and does not involve wakefulness, there are no reactions to light stimuli, endowed with different neurological symptoms, (loss of reflexes, without extrapyramidal hypertonia, and without a syndrome of pyramidal irritation), and other vegetative problems (hypothermia, stertorous respiration and rales as well as bradycarida). /1333

Biologically speaking, we can see:

- a hyperalcoholemia which is not accompanied by hyperglycemia;
- acidosis with high amounts of acetic acid, acetaldehyde and lactic acid;
- no hypernatremia.

Suffice it to say that these comas have in common a dehydration in connection with polyuria and hyperosmolality, the presence of moles of ethyl alcohol or glucose which largely determine this increase in osmolality.

These two molecules do not have a superposable effect in the development of these comas.

Glucose diffuses easily in almost all the cells of the organism, but by reason of hyperglycemia and the lack of insulin, the intracellular penetration will be slight and the osmotic pressure will rise. Since in the normal state the difference between glycemia and glycorachia is slight, in these comas the hyperglycorachia will only reach 50% of the hyperglycemia and the result will be a movement of water from the L.C.R. to the plasma. Glucose diffuses slowly but freely into the nerve cells and hyperglycemia does not cause troubles with consciousness.

Hyperglycemia causes an osmotic diuresis which is insensitive to ADH.

Dehydration and its consequences are therefore essential to the development of problems involving the "hyperosmolar" coma of the diabetic.

Ethyl alcohol diffuses freely in most tissues of the organism except for those cells which are rich in lipides.

It causes a water diuresis through inhibition of ADH; unlike glucose, it has a toxic effect with respect to the nerve centers.

CONCLUSIONS

Modern osmometers-cryoscopes operate on a principle involving the measurement of the decrease in the freezing point, allowing measurement of osmolality expressed in milliosmols/kg of water.

Numerous definitions of osmolality have been proposed.

The one which is the most classic makes osmolality and osmotic concentration synonymous. Dormandi [5] defines what he calls true osmolality, calculated osmolality, measureable osmolality and recorded osmolality.

While numerous definitions have been proposed and while numerous qualifications have been established in order to define a given term, it is a fact that the classical methods of measurement do not allow a proper appreciation of the forces which determine the osmotic pressure in the human organism. The semipermeability of cell membranes, the unequal permeability of a given cell membrane with respect to different molecules, the varying degrees of diffusion of these different molecules, at the level of the different tissues, as well as the inequal diffusion of a given molecule at the level of different tissues are the principal reasons which are responsible for the fact that a physical method cannot translate the osmotic pressure which is exerted in the organism.

We have used the term apparent osmolality to designate the measured value obtained with the aid of osmometers-cryoscopes which reflect the number of micro- or macromolecular particles existing in a biological fluid; apparent osmolality because all of the particles do not have the same osmotic pressure and this due to various factors which we have just discussed briefly; this is particularly true when we are speaking of a molecule such as ethyl alcohol. It possess a diffusion power which is high relative to certain cells (red blood cells for example), but it will diffuse with difficulty in tissues rich in lipides; its' osmotic pressure, the cellular dehydration which results from it, will therefore vary.

We have seen that a more or less significant ethanolization leads to a parallel increase in the apparent plasma osmolality; it is accompanied only rarely by a drop in the measured plasma resistivity (4 cases out of 50 subjects with alcoholemia above 1 g/l). The biological symptoms of dehydration with hemoconcentration (quantity of protides above 90 g/l) are exceptional: 2 cases out of 50.

Each time that it was possible, we studied the nature of the urine secreted at the time of the collection of the blood sample which was performed to measure alcoholemia and the plasma osmolality. These urine samples in most cases correspond to hypotonic polyuria. We have been able to verify that the releasing action of ethyl alcohol on the secretion of a hypotonic urine does take place, while alcoholemia and the apparent osmolality are only slightly increased; this results from an inhibition of ADH. /1334

Alcohol reduces the plasma tension with respect to antidiuretic hormone by inhibition of its release, without changing the possibility of its hypothalamic elaboration. The response of the renal tubules to this hormone remains normal (Bel [2]).

The repeated absorption of alcohol leads to the development of a polyuropolydipsic syndrome characterized by the significance of the polydipsia. Bel has shown that polyuropolydipsic alcoholics are potomaniacs and that the functional tests which have been carried out do not reveal the insufficiency of the secretion of antidiuretic hormone.

Following their acute intoxication, alcoholics who are drinkers of beer and wine compensate by drinking water (the vehicle for their alcohol) to compensate for dehydration, which could be the result of hypotonic polyuria; this is what explains our results.

It would not be the same if their intoxication were due to ingestion of pure alcohol.

REFERENCES

1. Abele, J.E., "Physical Chemistry Review," From Advanced Instruments Bulletin, O and M C7-11, 266-100, Newton, Massachussetts, 1965.
2. Bel, P., "Contribution to the Study of the Metabolism of Water and Electrolytes in Alcoholics," Doctoral Thesis, Lille, 1966.
3. Coreau, P., "On Perturbations of Cryoscopic Delta in Acute Alcoholic Conditions," Doctoral Thesis, Lyon, 1954.
4. Coulson, R., "The Osmometer in Clinical Diagnosis," From a talk presented to a New Orleans section of the American Society of Clinical Pathologists, printed by Advanced Instruments, Ref. 0-2, Coulson, Newton, Massachussetts, May 15, 1963.
5. Dormandi, T. L., "Osmometry," *The Lancet*, Vol. 1, No. 7484, pp. 267-270, 1967.
6. Fontan, M., Dujardin, J., Lecerf, J., Vanbatten, R., and M. Penot, "The Serum Albumin Space Labelled with I^{131} in Non-Cirrhotic Alcoholics," *Lille Médical*, Vol. 12, No. 4., pp. 432-442, 1967.
7. Fontan, M., Caridroit, M., Vaybon de la Moureyre, D., Fourlinnie, J.C. and P. Bel, "Dynamic Study of Hydro-electrolytic Disturbances in Chronic Alcoholics," *Lille Médical*, Vol. 12, No. 4, pp. 443-452, 1967.
8. Gamble, J.L., "An Economy in Renal Function Referable to Urine," *Am. Journ. Physiol.*, Vol. 109, pp.139, 1934.
9. Gram, H.C., *Amer. Journ. Med. Sci.*, Vol. 168, pp. 54, 1924.
10. Hamburger, J. and G. Mathe, Physiologie normale et pathologie due métabolisme de l'eau, (Normal Physiology and Pathology of Water Metabolism), Flammarion, Paris, 1952.
11. Hendry, E.B., "The Osmolality of Human Serum and of Chemical Solutions of Biological Importance," *Clin. Chem.*, Vol. 7, pp. 156, 1961.
12. Jacobson, M.H., Levy, S.E., Kaufman, R.M., Gallinek, W.E. and O.W. Donnelly, "Urinary Osmolality," *Arch. Intern. Med.*, Vol. 110, pp. 83-89, 1962.
13. Johnson, R.B. and H. Hoch, "Osmolality of Serum and Urine," *Standard Methods of Clinical Chemistry*, Vol. 5, pp. 159-168, edited by Academic Press, 1965.
14. Larcan, A., Boulange, M., Calamai, M. and P. Penin, "Research on the Mechanism of Hyperosmolar Comas in Diabetics," *Le Diabète*, Vol. 14, pp. 217-220, 1966.
15. Laroche, Cl., Caquet, R., Grégoire, J. and V. Luschevici, "On the Hyperosmolar Comas of Sugar Diabetes," *Sem. Hôp. Paris*, Vol. 22, pp. 1471-1489, 1967.
16. Lecocq, R., "Blood Cryoscopy in Chronic Alcoholism," *Comptes Rendus Acad. Sci.*, Vol. 252, No. 2, pp. 2325-2337, 1961.
17. Lecocq, R., "A Simple Means of Determining Alcoholic Impregnation of a Subject: The Cryoscopic Delta of the Blood," *Bull. Acad. Med.*, Vol. 147, pp. 21, 1963.

18. Lindeman, R.D., Van Buren, H.C. and L.G. Raisz, "Osmolar Renal Concentrating Ability in Healthy Young Men and Hospitalized Patients Without Renal Disease," *New Engl. J. Med.*, Vol. 262, pp. 1306-1309, 1960.
19. Mach, R.S., Les troubles du métabolisme due sel et de l'eau (Problems of Metabolism of Salt and Water), Masson, Paris, pp. 246, 1946.
20. Postic, F., Courtois, J. and Rabates, *Journ. of Pharm. and Chemi*, Vol. 8, No. 1, pp. 256, 1940.
21. Roberts, K., "Mechanism of Dehydration Following Alcohol Ingestion," *Arch. of Int. Med.*, Vol. 112, pp. 155, 1963.
22. Schwarzmann, V., Julie, N-cl., Borenstein, R., Eteve, J. and N. Bertaux, "Hepatic Alcohol Dehydrogenase in Alcoholics," *Rev . Franc. Etudes Clin et Biol.*, Vol. 7, pp. 762-765, 1962.
23. Sunderman, M. and Boerner, Normal Values in Clinical Medicine, Philadelphia, pp. 99., 1950.

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